



**Figure 12.13** PSI-353661 (**24**) and PSI-352938 (**25**) are liver-targeting prodrugs of 2'-fluoro-2'-C-methylguanosine 5'-monophosphate (**23**). PSI-353661 uses both a phosphoramidate prodrug strategy to mask the 5'-phosphate group and a C6-methoxy group to mask the polar nature of the guanine base. PSI-352938 utilizes a 3',5'-cyclic phosphate promoiety and C6-ethoxy promoiety on the guanine base. Both agents were developed for the treatment of HCV infection.

of 20%.<sup>60</sup> In HCV-infected patients, IDX-184 administered at doses from 25 to 100 mg qd over 3 days produced a maximum viral load decline of  $0.74 \log_{10}$  IU mL<sup>-1</sup> and a subsequent 14 day study in combination with pegylated interferon and ribavirin resulted in a  $2.7\text{--}4.1 \log_{10}$  IU mL<sup>-1</sup> reduction in viral load.<sup>61,62</sup> The PK and efficacy data clearly indicate that IDX-184 preferentially targets the liver.

Like IDX-184, BMS-986094 (**21**, Figure 12.12) demonstrated high dose-proportional liver levels of the same 2'-C-methylguanosine triphosphate in rats upon oral administration.<sup>56,63</sup> In portal vein-cannulated cynomolgus monkeys dosed orally with BMS-986094, the prodrug was observed in the portal vein but not in the systemic circulation, where only the 2'-C-methylguanosine metabolite was detected, thus supporting efficient liver extraction of the prodrug.<sup>56</sup> A Phase 1 study of BMS-986094 showed that the PK supported qd dosing and in HCV patients demonstrated a mean reduction in HCV RNA levels of 0.71 and  $1.3 \log_{10}$  IU mL<sup>-1</sup> at doses of 9 and 25 mg, respectively.<sup>64</sup> Unfortunately, BMS-986094 clinical trials were discontinued in August 2012 owing to severe cardiac adverse events. The underlying cause of the adverse events is not known; however, the natures of both the prodrug moiety and parent drug are under scrutiny. These adverse events have also resulted in a clinical hold on IDX-184 because both BMS-986094 and IDX-184 share the same active parent triphosphate although the prodrug substituents are different.